REMARKS

This Amendment responds to the Office Action mailed October 29, 2008. With this amendment, Applicants amend claims 3 and 5-8 and cancel claim 12. Applicants note that the Office has deemed claims 4, 10-11, and 13-32 as being directed to non-elected subject matter and therefore withdrawn these claims from consideration. Applicants note that claims 1 and 2 have been canceled previously. No new matter has been added with the present amendment. Support for the amendment can be found throughout the specification and claims as filed, including, e.g., in previously presented claims 3-32, and at page 13 of the specification. Claims 3 and 5-9 are pending and under consideration with this amendment.

Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 3, 5-9, and 12 as being indefinite for failing to particularly point out and distinctly claim the subject matter. For example, the Action rejects claim 3 for not reciting a nexus or connection between the preamble and detecting a gene polymorphism. In response, Applicants have amended the claims to recite that the presence of a polymorphism is indicative of the presence of an arteriosclerotic disease. Support for these amendments can be found in the specification, for example, at page 13. Applicants submit that the claims are sufficiently definite to ascertain their metes and bounds. In addition, applicants have canceled claim 12 to advance prosecution and without agreeing with or acquiescing to the rejection. As such, Applicants submit that this rejection no longer applies to claim 12.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Claim Rejections – 35 U.S.C. § 112, First Paragraph – Written Description

The Action rejects claims 3 and 5-9 as failing to comply with the written description requirement.

Specifically, the Action alleges that the specification does not sufficiently describe the claimed invention in a manner to convince one skilled in the art that the Applicants were in

possession of the invention at the time of filing. The Action also alleges that the previous claim amendments constituted new matter.

Without agreeing with or acquiescing to the rejection, Applicants note that claims 3, 5, and 6 have been amended to change "vascular inflammatory disease" to "arteriosclerotic disease." Applicants note that claims 7-9 depend directly or indirectly from the amended claims, and therefore, benefit from the amendments. These amendments find support in the specification, for example, at page 13.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Claim Rejections – 35 U.S.C. § 112, First Paragraph – Enablement

The Action rejects claims 3, 5-9, and 12, under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement.

Applicants respectfully submit that without expressing agreement with or acquiescence to the rejection claims 3, 5-9, have been amended. Claims 3, 5, and 6 have been amended to change "vascular inflammatory disease" to "arteriosclerotic disease." Applicants note that claims 7-9 depend directly or indirectly from the amended claims, and therefore, benefit from the amendments. These amendments find support in the specification, at for example, page 13. Applicants note that claim 12 has been canceled to advance prosecution and without agreeing with or acquiescing to the rejection. As such, Applicants submit that this rejection no longer applies to claim 12.

Applicants respectfully submit that the specification does enable a person skilled in the art to make and use the invention without undue experimentation. Arguments addressing the factors showing enablement follow.

Breadth of the Claims

The Action states that "the claims are broadly drawn to determining any vascular inflammatory disease by detection of SNP C/A polymorphism at nucleotide 80 in the nucleotide

sequence of exon 3 of the LT-α gene shown in SEQ ID no 3." The Action further states that "when the claims are read in light of the specification, the specification does not provide predictable guidance for any vascular inflammatory disease by detection of SNP C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID no. 3."

Applicants submit that the claims, as amended, are drawn to "determining an arteriosclerotic disease in humans, which comprises detecting a C/A polymorphism at nucleotide 80 in the nucleotide sequence of exon 3 of the LT-α gene shown in SEQ ID NO: 3, wherein the presence of the polymorphism is indicative of the presence of the arteriosclerotic disease." Further, Applicants note that the case-control association analysis in the present invention is based on data of Japanese people. However, the present invention should not be limited to Japanese people, as the present specification demonstrates that Thr26Asp polymorphism increases the activity of LTA (LT-α), and that the polymorphism 252A>G in intron 1 (in linkage disequilibrium) increases the expression level of LTA.

The function of LTA is described, for example, on page 2 of the specification. In view of the technical common knowledge at the time of filing of the present application, a person of skill in the art would know that a person having the aforementioned polymorphism has an increased level of inflammation in the diseased area (such as arteriosclerotic area). Polymorphisms, which are point mutations in genotypes, occur in humans as well as other animals, and are well known in the art. The presence of the aforementioned polymorphism is not dependent on race. The polymorphism described in the current invention has been found not only in Japanese humans, but also in Europeans and other races, as described in attached article from The PROCARDIS Consortium, European Journal of Human Genetics (2004) 12, 770-774 on page 771. In particular, this article notes that "[f]ive LTA SNPs in the linkage equilibrium (LD) block implicated in CAD in Japanese were confirmed to be polymorphic in our four white European populations." This reference is discussed in more detail in a subsequent section.

Nature of Invention

Applicants respectfully submit that the class of invention is diagnostics and molecular biology as well as population genetics. Generally speaking, prediction is difficult in some aspects of these fields of study. The present invention, however, is limited to the testing of a particular disease based upon a particular polymorphism. As discussed herein, the correlation between the polymorphism and the disease state is well established.

Teachings in the Specification and State of the Art

The Action states that the specification has not provided a predictable correlation of a specific SNP with any vascular inflammatory disease. Applicants believe that by limiting the disease to "arteriosclerotic disease" and removing "vascular inflammatory disease," the claim language more particularly defines the polymorphism and the associated disease, and this association is supported by the specification and the art. Applicants also submit that the skilled artisan would not be required to perform any undue amount of experimentation in order to practice the present invention.

Applicants note that the Action relies on the reference Witte et al. to show the lack of enablement for the present invention. In response, Applicants note that Witte et al. is a report on asthma, and does not relate to "arteriosclerotic disease." Thus, Witte et al. should not be relied upon to judge the enablement of the presently claimed invention.

The Action also relies on Tobin et al. (Eur. Heart J. 2004, Vol. 25, p. 459) to demonstrate a lack of enablement. The Action's position is that Tobin et al. demonstrates that the polymorphism does not correlate with the disease state, as claimed. The Action asserts, for example, on pages 9-10 that Tobin et al. teaches "that a correlation of the amino acid change represented by this SNP is not correlated to myocardial infarction" and "the correlation of myocardial infarction and the codon change T26N (threonine to asparagine) is not predicatable asscoated (Tobin et al.)."

Applicants disagree with the Action's interpretation of Tobin et al. Applicants note that when Tobin et al. is read as a whole, it makes clear that although it did not replicate the

association found in previous studies, the authors could not rule out the possibility of such associations existing. Tobin et al. states several reasons why its findings may differ from previous studies that found polymorphisms associated with risk of myocardial infarction and why its study should not rule out the possibility of associations:

> Some of the differences may relate to the nature of the population studied. Specifically, allele frequencies are known to vary significantly between Japanese and Caucasian populations. Methods of recruitment also need to be considered. All our cases were recruited after admission into hospital. If a polymorphism has an effect, not only on risk of event but also on acute survival, then this could obscure any association. Finally, although our study was adequately powered to detect a moderate effect of a gene with a minor allele frequency similar to that of the angiotensin converting enzyme polymorphism, the power is reduced with lower allele frequencies. ***Thus, the lack of replication of associations between less common polymorphisms and myocardial infarction that have been reported in previous studies in our study alone would not rule out the possibility of such an association.***

Tobin et al., page 465, emphasis added.

Further, Tobin et al. specifically states that "the lack of replication of associations between less common polymorphisms and myocardial infarction that have been reported in previous studies in our study alone would not rule out the possibility of such an association." Thus, Tobin et al. does not teach that the correlation of the myocardial infarction and the codon change Thr26Asn is not predictable; rather, Tobin et al. teaches that its study has "demonstrated the feasibility and utility of using a number of polymorphisms in linkage disequilibrium to assess the association between specific haplotypes and myocardial infarction in a study of unrelated individuals." Thus, rather than undermine the present invention, if anything, Tobin et al. supports the premise of the current invention that associations between polymorphisms and diseases are predictable.

However, Applicants wish to point out that Tobin et al. was not intended as a study for predicting a disease, but discloses the result of a case-control association analysis and the result of the association analysis of Europeans using only 500 patients and 500 controls. Thus, it cannot be compared directly with the present specification without taking into account

hierarchization of the samples. For this reason as well, it cannot be relied upon to show a lack of enablement of the present invention.

Applicants respectfully direct the Office's attention to an analysis using European peoples, The PROCARDIS Consortium, European Journal of Human Genetics (2004) 12, 770-774, which is provided with this response. In this article, the authors state that "the present study strongly reinforces the contention that [the LTA 252G/N26] haplotype, defined by at least three functional SNPs, may be causally related to MI [myocardial infarction] and/or CAD [coronary artery disease]." (Page 773). On page 772, the authors state that "[o]ur results, together with the Japanese case:control study, suggest that it is the 252G/N26-containing haplotype that is important *in vivo* in the MI/CAD association." Further, on page 771, the authors state that "[f]ive LTA SNPs in the linkage disequilibrium (LD) block implicated in CAD in the Japanese were confirmed to be polymorphic in our four white European populations."

Applicants note that the authors of The PROCARDIS Consortium study focused on the transmission disequilibrium test (TDT) (see page 773), and believed that the TDT was a better method versus the case:control study method for analyzing the association between polymorphisms of LTA and myocardial infarctions. In particular, the authors note that the problem of population stratification in case:control studies may be overstated, but recent data suggested that it still may be a significant problem. The issue of population stratification, which refers to differences in allele frequencies between cases and controls due to systematic differences in ancestry rather than association of genes with disease, also described as hierarchization, has been discussed when discussing case:control studies. (See Freedman et al. Nat Genet. 2004 Apr;36(4):388-93 (abstract)).

Applicants wish to point out that population stratification is not problematic for the Japanese population because Japanese people are known to be an almost uniform population, so a hierarchization test is not needed. When a population is not uniform, as with the European and American populations, the sample hierarchization is necessary when analyzing a possible polymorphism and disease association. Therefore, studies that use populations that are not uniform, like for example the study in Tobin et al., sample hierarchization needs to be conducted in order to make the findings more reliable.

Working Examples

The Action, on page 11, asserts that "it is unpredictable that there is a correlation of the allelic mutation based on the correlation of the homozygous 'AA' in the population." The Action relies on the specification and states that "the specification discloses that there is a predictable correlation of homozygous (AA) individuals with myocardial infarction compared to homozygous wild type (CC) and heterozygous (CA);" however, "the claims ... encompass detecting one 'A' allele."

Applicants respectfully submit that the field of polymorphism is characterized as a disease being in onset, or the probability of onset of the disease is high, when a person has a risk allele. In the present invention, when one allele has "A," then it is judged as a high risk; therefore, it is not necessary that both alleles have "A" (=AA) to determine that there is a high risk. When data of patients are used, there are combinations of AA, AC, and CC.

Applicants note that the specification includes working examples, and that these working examples support the presently claimed invention.

Predictability and Unpredictability of the Art and Degree of Experimentation

The Action, on page 12, states that the "[p]ost-filing art teaches that SNPs in LT-A are not strongly associated with any vascular inflammatory diseases," referring to Witte et al., Trabetti et al., and Newton-Cheh et al.

Initially, Applicants respectfully note that SNPs in LTA are associated with arteriosclerotic diseases and the current claim amendments add "arteriosclerotic disease" and removes "vascular inflammatory disease."

The Office Action states that Witte et al. "teaches detection of the LT-A SNP of the first intron NcoI recognition sequence in asthma and nonasthmatic patients (abstract)" and that "no statistically significant correlation between this SNP and asthma []. Therefore Witte et al. teaches that LT-A mutations are not associative to any inflammatory disease." Applicants again

respectfully note that Witte et al. discusses asthma and not arteriosclerotic disease. Therefore, any conclusions or findings stated in Witte et al. cannot be applied to the present invention.

The Action states that Trabetti et al. "teaches an association of atopy in asthma patients and the LT-A NocI SNP (abstract)" and "[h]owever, Trabetti et al. teaches this same association in other populations (Busselton population) was not observable []. Therefore Trabettti et al teaches that in different populations the association of the LT-A mutation with a specific disease is not correlative." As with Witte et al., Applicants respectfully note that Trabetti et al. discusses asthma and atopy, and not arteriosclerotic disease. Therefore, any conclusions or findings stated in Trabetti et al. cannot be applied to the present invention.

The Action cites Newton-Cheh et al. for the proposition that "myocardial infarction is a complex trait to which multiple environmental and genetic factors contribute" and that "there is evidence that there are sex differences between male and females with regard to correlation of genetic variants in myocardial infarction (p. 3008 3rd paragraph). Therefore the art teaches the unpredictability of such associations in different populations."

With regard to Newton-Cheh et al., Applicants note that Newton-Cheh et al. discuss the difference between sexes based on the polymorphism of estrogen receptor, specifically estrogen receptor alpha (ESR1). Applicants note that the difference between sexes is expected in Newton-Cheh et al. since estrogen is a sex hormone. Newton-Cheh et al. describe the difficulty of case-control association analysis, and do not state that onset of disease cannot be predicted by other polymorphism outside of ESR1. Therefore, Newton-Cheh et al. does not preclude that the polymorphism of LTA is associated with arteriosclerotic disease, specifically myocardial infarction.

The Action also asserts on page 13, that Tobin et al. does not teach a statistically significant p-value for SNP T26N and that "the differences in association might be due to the different types of populations" and that "the statistically significant association of the SNP with myocardial infarction in the instant specification [] is not reproducible in other populations."

Applicants again disagree with the Action's interpretation of Tobin et al. When read as a whole, Tobin et al. says that although its study did not replicate the association found in previous

studies, that its study alone could not rule out the possibility of such associations existing. Applicants further submit that Tobin et al. uses a non-uniform population, specifically European, for its association studies, thereby likely displaying the problem of population stratification in case:control studies mentioned above. The statistical differences in p-values between Tobin et al. and the present invention is likely explained by the different populations used and Tobin et al. not using a hierarchization test to account for the population not being uniform.

Applicants submit that Tobin et al. explains why its finding differs from previous findings, where LTA polymorphisms were associated with arteriosclerotic disease, such as myocardial infarction. Applicants also submit that the alleged unpredictability cited by the Office in the post-filing references Witte et al. and Trabetti et al. were not relevant in that they focused on either asthma and/or atopy rather than arteriosclerotic diseases. Applicants further submit that the alleged unpredictability discussed in Newton-Cheh et al. is not relevant to the present invention because it focuses on the difference between the sexes based on the polymorphism of estrogen receptor, which is a sex hormone, and does not discuss LTA specifically.

In view of the foregoing, Applicants respectfully submit that the specification provides an adequate amount of direction and guidance to perform this invention without undue experimentation. Applicants respectfully request withdrawal of the rejections.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to withdraw the rejections of record and allow all the pending claims.

Applicants invite the Examiner to contact the undersigned with any questions.

Respectfully Submitted,
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